REMARKS/ARGUMENTS

The abstract has been rewritten as required, and the specification has been amended to avoid the use of multiple inconsistent terms in connection with reference numbers 4, 5, 6 and 7.

Claim 9 has been amended to avoid the indefiniteness arising as a result of the absence of antecedent basis for the term "injection step," and by reason of the discrepancy in terminology pointed out by the Examiner.

Claim 10 has been canceled.

Claim 11 has been amended to change "2(c)" to --(c)-- as suggested by the Examiner, and to eliminate the indefinite term "or the like."

Claim 1 has been amended to clarify the reference to the channels and their openings, and recite the multi-port valve and its relationship to the channels as will be discussed more fully below. New claims 13 and 14 have been added.

The amendments to claim 1 are supported in the description (page 3, paragraph beginning at line 29, for "mechanically manipulating fluid samples" and "controlling the flow direction in all arms" of the intersection formed by the first and second channels; page 9 line 2 and 27 for the "eight-port valve.") The description at pages 10-15 establishes that the 8 port valve is the sole actuator, that is, only the 8 port valve is actuated to direct the fluid flows in the various arms of the intersection.

The new claims 13 and 14 set forth further details of the embodiments depicted respectively in Figures 2 and 5 and the related descriptions. These claims specifically define the

flow paths and closed loops provided in the two alternative positions of the multi-port valve having at least eight ports.

Similarly to Chien et al. and Liu et al., the present invention provides a novel means of controlling fluid flows in a microchannel network having fluidic communication by way of an intersection. In the present invention, however, fluid transport is entirely controlled by mechanical means, which is new over Ramsey I, Chien et al. and Liu et al., all of which require electrokinetic pumping and hence application of a electric potential in the various branches of the microchannel network.

The Examiner points out that these systems are fully controlled by electrical means. However, there are fundamental differences between mechanical and electrokinetic pumping. No pressure is applied during electroosmosis. Rather, the movement of fluid is generated by charge displacement at the walls of the conduits, and is not due to a pressure difference. This fundamental difference is illustrated by the profiles of the fluid flow, which are convex for convective flows (pressure induced fluid movement) as shown in Applicants' FIG. 5(b), and straight for electroosmotic flows, as shown in Ramsey's FIGs. 5(a)-5(c). As noted by the Examiner at page 6 lines 12-14 of the Office action, any movement of fluid is accompanied by a pressure differential. However, cause and effect should not be confused. In electrokinetic pumping, the fluid movement is caused by the charge displacement induced by the application of a potential difference along the channel; in mechanical pumping, the fluid movement is caused by the application of a pressure difference along the channel. Both phenomena are

accompanied a pressure differential, but their origin, and hence the means used to generate them, are totally different.

On page 5, line 20 of the Office action, the Examiner interprets Ramsey as teaching the application of pressure ("while applying pressure to channels 30 and 32"). However, Ramsey is restricted to an apparatus in which all fluid manipulations are controlled by electrical potential application, and the features of Fig. 31 of Ramsey are also subject to this condition. Ramsey's description specifies, at column 33 lines 48-49 that "the voltages applied to the solvent reservoirs 12, 14 are changed as a function of time. . .". There is no inter-relation between mechanical (or pressure) pumping and electrokinetic pumping, and thus a document such as Ramsey's patent, solely concerned with electrokinetic fluid manipulation, does not teach anything about controlling fluid movement by mechanical means. The invention relies on a physical phenomenon totally different from that of Ramsey.

In addition, electrokinetic pumping is limited to salt-containing solutions, and the accuracy of the electrokinetic injection is dependent on the sample composition, since the electroosmotic flows necessitate ion-containing solutions and the intensity of the electroosmotic flows varies with concentration and conductivity. Based on pure mechanical pumping means, the device of the present invention is suitable for controlling the movements of any kind of solution (even pure water or nonpolarizable organic solvents). This is a highly advantageous feature, which cannot be achieved with electrokinetic pumping means, and which overcome the main

drawbacks of electroosmosis-based microfluidics, for example prevention of on-line electrospray mass spectrometry analysis.

On the other hand, the flow profiles that are obtained with electrokinetic pumping are better suited for injection of small solution plugs and microfluidic manipulations than those obtained by mechanical pumping, where the convective flow profile generally leads to dispersion and less efficient separations. It is thus a real challenge to control mechanical flows and to perform injections of well-defined sample plugs in microchips. The invention provides a device and method to do this efficiently.

The fact that pinched injection is known from Ramsey with electroosmotic pumping does not explain how such injection can be performed by pure mechanical means. The fact that others may use a valve to fill-in a microchannel (as with the gating channel of Jorgensen) does not indicate how a multiport valve can be combined with a microchannel network in order to control fluid flows by mechanical means only. A combination of Ramsey and Jorgensen does not teach how the device of the invention can be built, nor how it can work.

Knapp et al. mention microfabricated fluid pumping and valving systems, but state that these are not preferred for reasons of cost and complexity - see column 50, lines 62 to 67. Thus, Knapp et al. also focus on electrokinetic systems,

Jorgensen relates to a device comprising a gating channel enabling the deviation of the flow of an upstream effluent in order to prevent its entry into a downstream channel. The multi-port valve used in this system only serves to supply or block a flush solution to the gating channel. There is no

information about how such a multi-port valve may be connected to the entire microchannel network in order to create a sample injection system with controlled, mechanically-driven fluid pumping. In the present invention, the special connection of the various branches of the microchannel network and their disposition in the multi-port valve allows the control of the microfluidics in all branches of the channel intersection and the injection of solution plugs similarly to what can be achieved with pinched electrokinetic injection, but without the need for any potential application, and solely by actuation of an 8-port valve. As set forth in claim 1, as amended, the "multi-port valve" has "at least eight ports" and is "the sole actuator controlling the direction of flow of fluid samples in all the arms of said intersection, and controlling the directions of flow in all of said arms simultaneously."

The principle of sample introduction using the gating channel of Jorgensen is completely different from that used in the present invention. In Jorgensen, only the effluent channel is connected to the multi-port valve, whereas, in the present invention, at least three openings of a 4-branch microchannel network have to be connected to such a valve. In Jorgensen, there is a continuous fluid flow in the upstream effluent channel, and the flush solution allows a change in the direction of this fluid flow so as to prevent its entry into a downstream effluent channel. The multi-port valve simply serves as a on/off switch for inducing a flow of flush solution, and there is nothing in Jorgensen describing how a multi-port valve may be combined with an interconnected microchannel network to control the fluidics simultaneously in

all the branches of the network. In addition, Jorgensen does not allow pinched injections.

In addition, the device of the invention also allows simplified instrumentation for injection with convective fluid flows. In Chien et al. for instance, each reservoir is connected to a syringe pump, and the pressure applied in each syringe is fixed by a controller. In the invention as defined in claims 13 and 14, however, at least two of the four branches of the micro-channel network are connected together through the multi-port valve, so as to form a "closed loop" that ensures equal pressure in this pair of channel branches. This cannot be achieved with the device of Chien et al., which has individual pumping means in all branches of the network.

With the device of the invention, the liquids may be directed in any direction within the microchannel network, depending on the way the various branches of this network are connected to the multi-port valve. For instance, the fluids can be pinched in the separation channel, which is not feasible with the apparatus of Jorgensen, in which the direction of the fluid flow in the upstream effluent channel cannot be opposite to that in the downstream effluent channel. The main advantage of the invention over all of the cited prior art documents is the fact that it allows fully mechanically-driven injection with microfluidic control in all the branches of a microchannel network. This is achieved using a multi-port valve having at least 8 ports, which enables synchronisation of all pressures and all fluid flows in all branches of the microchannel network. The actuation of a single 8-port valve enables stopping, moving or reversal of the fluxes in each branch of

the microchannel network, without modification of the applied pressures. This is a significant advance over the prior art. Indeed, by using the gating system of Jorgensen, notably the 6-port valve of Fig. 2, it is not possible to actuate the fluxes in all the channel branches simultaneously, since neither channel 34 nor channel 35 is dependent on the actuation of the 6-port valve. With the system of Jorgensen, it is impossible to control the pressure distribution in the various channels and to perform the pinched mechanical injection described in the present application. In fact, Jorgensen's system is not complete, and necessitates coordination between the valve 41 and the pumping system used to drive the fluids in channel 35. There is no means of controlling the flux in channel 35, even if channel 34 is connected to the multi-port valve.

Jorgensen's gating system allows the diversion of fluid flow from channel 34 to channel 38 (to prevent its entry into channel 35), but it has no influence on the pressure - and hence the fluid flow - in the upstream channel 34. Therefore, this system is not suited for fully controlled microfluidic manipulations; it is not of real interest for microchips, because it also generates significant dead volumes.
The device of the present invention overcomes these drawbacks by enabling an accurate control of the fluid flows in all branches of a microchannel network. In addition, it greatly simplifies the instrumentation, which is a significant difference over all cited prior art.

In summary, the system described in Jorgensen (which the Applicant considers the closest prior art) does not allow the

control, blocking, initiation or reversal of fluid flow in the channels 34 or 35, and the combination of the various elements of Fig. 2, even when used in a manner different from that described, does not allow the control, by the actuation of a single multi-port valve, of the fluxes in each channel and, hence, the mechanical injection of a sample plug.

For the reasons set forth above, and in view of the amendment to claim 1 herein, it is respectfully submitted that the claims now define subject matter that is neither anticipated, nor shown to have been obvious, by the art of record. Favorable reconsideration and allowance of this application are requested.

Respectfully submitted,
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